UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: November 9, 2011

SUBJECT: AMINOCYCLOPYRACHLOR: Report of the Cancer Assessment Review Committee

PC Code: 288008
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Cancer Assessment
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FROM: Jessica Kidwell, Executive Secretary Jessica Kidwell
Cancer Assessment Review Committee
Health Effects Division (7509P)

THROUGH: Jess Rowland, Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Jessica Ryman, Toxicologist
RAB IV, Health Effects Division (7509P)

Kable Bo Davis, PM 25
Herbicide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on August 17, 2011 to evaluate the cancer classification of Aminocyclopyrachlor in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

Aminocyclopyrachlor

PC Code 288008

Final
November 9, 2011

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Jessica Ryman, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Lori Brunsman

Marion Copley

Kit Farwell

Ray Kent

Karlyn Middleton

Jess Rowland, Chair

P.V. Shah

Yin-Tak Woo

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist

OTHER ATTENDEES: Jonathan Chen (AD), Uma Habiba (HED)

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EXECUTIVE SUMMARY

On August 17, 2011, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of aminocyclopyrachlor.

Jessica Ryman of Risk Assessment Branch IV presented the chronic toxicity/ carcinogenicity study in rats (MRID 48333607) and the carcinogenicity study in mice (MRID 48333606). Aminocyclopyrachlor technical was administered to Crl:CD(SD) rats (70/sex/dose) at dietary dose levels of 0, 600, 2000, 6000, or 18000 ppm (0/0, 27/29, 97/100, 279/309, 892/957 mg/kg bw/day in males/females) for 2 years to assess carcinogenicity. A satellite group of animals (10/sex/dose) was sacrificed at one year to assess chronic toxicity. Aminocyclopyrachlor was administered to young adult male and female Crlj:CDl(ICR) mice (60/sex/group) in diets that contained 0, 300, 1000, 3000, or 7000 ppm DPX-MAT28 for approximately 18 months. This corresponded to doses of approximately 0/0, 39/50, 133/171, 393/527, and 876/1190 mg/kg bw/day in males/females. Mutagenicity data and structure activity relationship data were also discussed.

The Committee considered the following for a weight-of-evidence determination of the carcinogenic potential of aminocyclopyrachlor.

Carcinogenicity

Rat

• *Brain Tumors:* The CARC concluded that the brain tumors (glial cell tumors and granular cell tumors) observed in male rats were spontaneous lesions and were <u>not</u> considered to be treatment-related. This was based on the following weight-of-evidence considerations: 1) Although there were significant trends and pair-wise comparisons at the high dose for astrocytomas and glial cell tumors combined by the Peto analysis, the incidences were within the historical control range. For granular cell tumors, there was a significant trend only, but no significant pair-wise comparison of any dose group with the controls. In addition, the Fishers Exact test showed trends only and no pair-wise comparisons of any dose level with the controls for combined glial tumors and for granular cell tumors. 2) No supporting treatment-related pre-neoplastic lesions were observed in the brain (or any other tissue). (Chemicals known to cause brain tumors also are commonly tumorigenic in other tissues, J. Pletcher, Consulting Pathologist, Personal Communication); 3) The tumors occurred at the limit dose; no other tumors were seen; 4) No treatment-related brain neoplastic lesions were observed in female rats. 5) No evidence of genotoxicity was observed in *in vitro* or *in vivo* genotoxicity studies. 6) Brain levels of radioactivity after administration of aminocyclopyrachlor at times corresponding to peak plasma concentration were very low (<0.01%) and were undetectable after 72 hours.; 7) the Pathology Peer Review also concluded that the brain tumors were spontaneous tumors and not treatment-

related (MRID 48333607).

• *Adequacy of Dosing:* Dosing was considered adequate, and not excessive, for assessing carcinogenicity since the high dose approached the limit dose in both sexes (892/957 mg/kg bw/day in males/females). The high dose also caused mild decreases on body weight (decrease up to 12%) and body weight gain (decrease up to 11%) in both sexes during the study, but had resolved by the conclusion of the study.

Mouse

• There were no treatment-related increases in tumor incidences in either sex.

• *Adequacy of Dosing:* Dosing was considered adequate since the high dose in this study approached the limit dose (876/1190 mg/kg/day in males/females). No adverse effects (including changes in body weight) were observed at this dose level.

Mutagenicity: There is no concern for mutagenicity.

Structure Activity Relationship: There is no sufficient basis for SAR concern.

Classification and Quantification of Carcinogenic Potential

In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified aminocyclopyrachlor as “Not Likely to be Carcinogenic to Humans.” There were no treatment-related tumors seen in male or female rats or mice at doses that were adequate to assess carcinogenicity. There is also no concern for mutagenicity.

Quantification of carcinogenicity is not required.

I. INTRODUCTION

On August 17, 2011, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of aminocyclopyrachlor.

II. BACKGROUND INFORMATION

Aminocyclopyrachlor is a pyrimidine carboxylic acid herbicide that was registered for non-food use in 2010. It is now being registered for the first food use on rangeland, pastures, and Conservation Reserve Program (CRP) acres. There are three forms of aminocyclopyrachlor: the parent acid (PC Code 288008), the potassium salt (PC Code 288010), and the methyl ester (aminocyclopyrachlor-methyl, PC Code 288009). All three forms are components of both manufacturing and end-use products. Aminocyclopyrachlor is considered the active ingredient due to rapid hydrolysis of aminocyclopyrachlor-methyl to aminocyclopyrachlor by cellular esterases. The pesticidal mode of action of aminocyclopyrachlor is dysregulation of gene products involved in auxin receptor activity, which interferes with normal shoot and root development to stop the growth of weeds.

The only tumors observed in chronic toxicity/carcinogenicity studies in two species were brain tumors in male rats. The registrant contends that these tumors are not treatment-related, based on a consensus opinion following peer review by six board-certified pathologists.

Aminocyclopyrachlor (a.i.)	Aminocyclopyrachlor-methyl (methyl ester)	Aminocyclopyrachlor, K salt (Parent acid)

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Moon, Kyoung. (2010). DPX-MAT28 Technical: Carcinogenicity 2-Year Feeding Study in Rats. Korea Institute of Toxicology, Daejeon, Republic of Korea. Laboratory Study Number: IG07280, November 24, 2010, MRID 48333607. Unpublished.

A. Experimental Design

Aminocyclopyrachlor technical (DPX-MAT28, Lot/batch# J-868-001-3, Purity 88.3-90.5%) was administered to Crl:CD(SD) rats (70/sex/dose) at dietary dose levels of 0, 600, 2000, 6000, or 18000 ppm (0/0, 27/29, 97/100, 279/309, 892/957 mg/kg bw/day in males/females) for 2 years to assess carcinogenicity. A satellite group of animals (10/sex/dose) was sacrificed at one year to assess chronic toxicity.

B. Statistical Analysis by HED

Brain tumors were observed only in male rats. No tumors were observed in female rats or in mice of either sex. Statistical analyses were run on male rat mortality and brain tumor data.

C. Discussion of Survival Data

There was no statistically significant trend in mortality with increasing doses of aminocyclopyrachlor in male rats; however, there was a statistically significant negative pair-wise comparison of the 600 ppm dose group with the controls at $p < 0.05$ (Table 1) (TXR No. 0055738).

Table 1. Aminocyclopyrachlor – Crl:CD(SD) Rat Study (MRID 48333607)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	52[i]	53-78	79-105[f]	Total
0	1/80	1/79	10/78	12/68	29/56	43/70 (61)
600	0/80	0/80	10/80	14/70	17/56	31/70 (44)[*n]
2000	3/80	6/77	10/71	8/61	28/53	45/70 (64)
6000	0/80	4/80	10/76	10/66	33/56	47/70 (67)
18,000	0/80	3/80	10/77	6/67	25/61	34/70 (49)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 52.
[f]Final sacrifice at weeks 104-105.
[n]=negative pair-wise comparison with control
( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If [*], then $p < 0.05$. If [**], then $p < 0.01$.

D. Neoplastic lesions

Male rats had statistically significant trends at $p < 0.01$, and significant pair-wise comparisons of the 18,000 ppm dose group with the controls at $p < 0.05$, for (malignant) brain astrocytomas and combined astrocytoma, glioma and oligodendrogliomas. There were statistically significant trends in (malignant) brain gliomas at $p < 0.05$ and in brain granular cell tumors at $p < 0.01$. It should be noted that the first brain glioma was observed at week 50 and that only week 52 interim sacrifice animals in the control and 18,000 ppm dose groups were examined. All interim sacrifice animals are considered to be "at risk" since the interim sacrifice occurred after week 50, therefore, all interim sacrifice animals should have received full histopathological evaluations. Potentially more animals could have had tumors which would have been diagnosed if these animals had been examined. The statistical analyses of the tumors in the male rats were based upon Peto's Prevalence Test (Tables 2a and 2b) (TXR No. 0055738).

Since the effect on survival was not dose-related, the statistical analyses of the brain tumors in male rats were also run using the Fisher's Exact Test and Exact Test for Trend. For combined glial cell tumors and the granular cell tumors, there was a statistically significant trend only, but no significant pair-wise comparison at any dose (Tables 3a and 3b).

Table 2a. Aminocyclopyrachlor – Crl:CD(SD) Rat Study (MRID 48333607)

Male Brain Tumor Rates[+] and
Peto's Prevalence Test Results

	Dose (ppm)				
	0	600	2000	6000	18,000
Astrocytomas (%) p =	0/64 (0) 0.00130**	0/66 (0) -	0/60 (0) -	1/65 (2) 0.16290	3[a]/65 (5) 0.03760*
Gliomas (%) p =	0/78 (0) 0.02052*	0/70 (0) -	0/62 (0) -	0/66 (0) -	1[b]/78 (1) 0.12883
Oligodendrogliomas (%) p =	0/27 (0) 0.48486	0/39 (0) -	0/25 (0) -	1[c]/22 (5) 0.13397	0/36 (0) -
Combined (%) p =	0/78 (0) 0.00058**	0/70 (0) -	0/62 (0) -	2/66 (3) 0.07203	4/78 (5) 0.01696*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First astrocytoma observed at week 63, dose 18,000 ppm.
[b]First glioma observed at week 50, dose 18,000 ppm.
[c]First oligodendroglioma observed at week 105 in an interim sacrifice animal, dose 6000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data from the performing lab (taken from p. 42 of the Study Report)

- Malignant Astrocytoma: Incidence†: 26/2146 (1.21%), Range (per study): 0-4.9%
- Malignant Glioma[a]: Incidence†: 3/2146 (0.14%), Range (per study) 0-1.92%
- Malignant Oligodendroma: Incidence†: 3/2146 (0.14%), Range 0-2.0%

†2146 male brains examined in 30 carcinogenicity studies
[a]including "undifferentiated glioma"

Table 2b. Aminocyclopyrachlor – Crl:CD(SD) Rat Study (MRID 48333607)

Male Brain Tumor Rates[+] and
Peto's Prevalence Test Results

	Dose (ppm)				
	0	600	2000	6000	18,000
Granular Cell Tumors (%)	0/35 (0)	0/42 (0)	0/35 (0)	0/34 (0)	2[a]/40 (5)
p =	0.00190**	-	-	-	0.05452

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First granular cell tumor observed at week 98, dose 18,000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data

- Granular cell tumors: Incidence: 8/2146 (0.37%), Range: 0-2.0%

Table 3a. Aminocyclopyrachlor – Crl:CD(SD) Rat Study (MRID 48333607)

Male Combined Brain Tumor Rates[+]
(Astrocytomas, Gliomas and Oligodendrogliomas) and
Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)				
	0	600	2000	6000	18,000
Combined (%)	0/78 (0)	0/70 (0)	0/62 (0)	2/66 (3)	4[a]/78 (5)
p =	0.00349**	1.00000	1.00000	0.20833	0.06009

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First tumor observed at week 50, dose 18,000 ppm.

Table 3b. Aminocyclopyrachlor – Crl:CD(SD) Rat Study (MRID 48333607)

Male Brain Tumor Rates[+] and
Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)				
	0	600	2000	6000	18,000
Granular Cell Tumors (%)	0/68 (0)	0/70 (0)	0/61 (0)	0/66 (0)	2[a]/66 (3)
p =	0.03927*	1.00000	1.00000	1.00000	0.24071

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First granular cell tumor observed at week 98, dose 18,000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Pathology Peer Review

The registrant contends that the brain tumors observed in male rats were not treatment-related. This conclusion was reached after a Pathology Peer Review Group organized by Experimental Pathology Laboratories, Inc. (Sterling, VA USA) was convened in order to review the brain histopathology and interpret the findings. (Note: this group is referred to in the Study Report as a Pathology Working Group (PWG). Although this Group followed the Agency's guidance for conducting a PWG in 83-6, the Group was convened *before* the Study Report was written and not afterward. As such, the Group's expert opinion is incorporated into the Study Report and is not a separate document. To avoid confusion, this group is referred to herein as a Pathology Peer Review Group). This Group was composed of 5 independent consulting pathologists with expertise in rodent toxicity and carcinogenicity studies, and with specific expertise in neuropathology. A sixth pathologist with similar background served as the chairperson and author of the final report. All of the brain histopathology slides were independently reviewed by one of the Group pathologists prior to the Pathology Peer Review Group meeting to confirm the findings of the Study pathologist. During the Group's meeting, the brain slides with neoplastic findings were coded and reviewed by each panel member. Following this independent review, the panel members reached consensus on the diagnosis for each slide and conducted a weight-of-evidence evaluation to determine if any histopathological findings were spontaneous or associated with test substance administration.

The Pathology Peer Review Group concluded that the astrocytomas in the high dose males were not treatment related. The basis for this conclusion was:

- No evidence of non-neoplastic glial cell proliferation caused by the test substance in male or female rats at any dose.
- No decrease in tumor latency in the high dose groups compared to other treatment groups with tumors.
- The age of onset of astrocytomas (Days 393-728) were consistent with age-related neoplasms.
- No treatment-related brain neoplasms were observed in female rats.
- No preferential accumulation of aminocyclopyrachlor in the brain as compared to other tissues.
- No evidence of genotoxicity was observed in genotoxicity assays.

The full Report of the Pathology Peer Review Group is available in MRID 48833607.

E. Non-neoplastic lesions

All non-neoplastic lesions in the 1-year interim sacrifice animals and in the 2 year main study group animals were consistent with background lesions that are typical of rats of this age and strain.

F. Adequacy of Dosing for Assessment of Carcinogenicity

Dosing was adequate, and not excessive, for assessing carcinogenicity since the high dose approached the limit dose in both sexes (892/957 mg/kg bw/day in males/females). The high dose also caused mild decreases on body weight (decrease up to 12%) and body weight gain (decrease up to 11%) in both sexes during the study that had resolved by the conclusion of the study (see Table 4 below).

Table 4 –Body weights (BW)

g±SD	0	600 ppm	2000 ppm	6000 ppm	18,000 ppm
MALES initial BW	216.3 ±12.82 (N=80)	216.2 ±12.27 (N=80)	216.3 ±11.34 (N=80)	210.4 ±10.40 (N=80)	214.2 ±10.70 (N=80)
Day 189	656.3 ±63.25 (N=79)	664.0 ± 72.90 (N=80)	664.3 ±75.47 (N=79)	647.8 ±81.24 (N=80)	616.8 ±56.79** (↓ 6%) (N=80)
Day 385	813.2±81.11 (N=67)	816.1±86.22 (N=69)	819.7±108.73 (N=61)	820.2±113.91 (N=66)	751.5±81.69** (N=66) (↓ 8%)
Day 539	860.0±115.31 (N=57)	877.0±114.69 (N=59)	870.6±116.75 (N=54)	884.5±155.21 (N=59)	801.9±124.85** (N=63) (↓ 7%)
Final BW	877.3±139.43 (N=27)	879.3±152.83 (N=39)	856.2±170.70 (N=27)	840.9±165.12 (N=25)	788.5±163.19 (N=36)
FEMALES Initial BW	158.7±9.65 (N=80)	158.6±8.74 (N=80)	157.1±8.94 (N=80)	155.0±8.39* (N=80) (↓2%)	154.2±9.90** (N=80) (↓3%)
Day 189	345.8±40.75 (N=80)	349.5±34.08 (N=80)	349.6±31.11 (N=79)	346.2±32.50 (N=80)	324.2±28.47** (N=79) (↓6%)
Day 385	441.9±80.88 (N=66)	438.3±68.10 (N=69)	441.7±68.40 (N=68)	445.6±53.91 (N=69)	402.7±54.09** (N=66) (↓9%)
Day 539	505.1±111.38 (N=59)	500.2±98.55 (N=52)	503.6±98.90 (N=54)	500.8±73.09 (N=54)	442.5±72.41** (N=56) (↓12%)
Final BW	535.2±153.47 (N=27)	538.7±82.23 (N=27)	533.3±121.84 (N=25)	518.8±86.13 (N=26)	487.3±85.64 (N=23)

*Significant differences from control at $p<0.01$
**Significant differences from control at $p<0.01$

2. Carcinogenicity Study in Mice

Jung-Im Huh, Ph.D. (2010). DPX-MAT28 Technical: Carcinogenicity 18-Month Feeding Study in Mice. Korea Institute of Toxicology, Republic of Korea. Laboratory Study Number: IG07280, October 15, 2010 MRID 48333606. Unpublished.

A. Experimental Design

Aminocyclopyrachlor (Batch/Lot# J-868-001-3, Purity 88.3-90.5%) was administered to young adult male and female Crlj:CDl(ICR) mice (60/sex/group) in diets that contained 0, 300, 1000, 3000, or 7000 ppm DPX-MAT28 for approximately 18 months. This corresponded to doses of approximately 0/0, 39/50, 133/171, 393/527, and 876/1190 mg/kg bw/day in males/females.

B. Discussion of Survival and Tumor Data

The performing laboratory did not find any treatment-related changes in survival in either sex. There were also no treatment-related increases in tumor incidence in either sex. Therefore, no in-house statistical analyses were performed.

C. Non-neoplastic lesions

All non-neoplastic lesions were consistent with background lesions that are typical of mice of this age and strain.

D. Adequacy of Dosing for Assessment of Carcinogenicity

The high dose in this study approached the limit dose (876/1190 mkd in males/females). No adverse effects (including changes in body weight) were observed at this dose level. Dosing was considered adequate and not excessive.

IV. TOXICOLOGY

1. Metabolism

Pharmacokinetic studies in rats show that both aminocyclopyrachlor and aminocyclopyrachlor-methyl are rapidly absorbed, with peak concentrations occurring in plasma and red blood cells (RBCs) at 0.3-1.0 hours for aminocyclopyrachlor and at 0.3-0.6 hours after dosing for aminocyclopyrachlor-methyl. Aminocyclopyrachlor-methyl was rapidly metabolized to aminocyclopyrachlor (within 30 minutes). No other metabolites were identified for either compound. The areas under the curve (AUCs) for both compounds scaled with dose, indicating that metabolic processes were not saturated. The (plasma) elimination half-life of aminocyclopyrachlor of 5.6-5.7 hours was shorter than that for aminocyclopyrachlor-methyl at

8.7-13.3 hours. The majority of the administered dose of both compounds was excreted within 24 h, although elimination differed slightly. For aminocyclopyrachlor, 35.8-53.71% was eliminated in the urine and 31.4-48.0% was eliminated in the feces. For aminocyclopyrachlor-methyl, the majority was recovered in the urine 78.80-78.82%, with a smaller amount eliminated in the feces (1.72-4.57%). Neither aminocyclopyrachlor nor aminocyclopyrachlor-methyl was eliminated as expired air. No sex differences in absorption, distribution, metabolism, or excretion were observed for either aminocyclopyrachlor or aminocyclopyrachlor-methyl.

Repeated-dose metabolism studies with aminocyclopyrachlor and aminocyclopyrachlor-methyl showed that radioactivity was found primarily in the GI tract and GI contents, with brain levels of radioactivity at less than 0.01% at the peak time after administration. Brain levels of radioactivity were undetectable after 72 hours.

2. Mutagenicity

Genotoxicity studies were conducted using aminocyclopyrachlor or aminocyclopyrahclor-methyl as the test material (Table 5). For aminocyclopyrachlor, there was no evidence of induced mutant colonies over background in the presence or absence of S9 activation in *in vitro* bacterial or mammalian gene mutation assays. There was also no evidence of chromosomal aberrations induced over background in the presence or absence of S9 activation *in vitro*. *In vivo*, there were no increases in the frequency of micronucleated polychromatic erythrocytes in bone marrow.

For aminocyclopyrachlor-methyl, in vitro bacterial gene mutation studies showed no evidence of mutant colonies over background in the presence or absence of S9 activation.

Together, these studies indicate that aminocyclopyrahclor-methyl and aminocyclpyrahclor are not genotoxic.

Table 5-Genotoxicity Studies		
Aminocyclopyrachlor		
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47560019 (2007) Acceptable/guideline 0, 50, 150, 500, 1500, or 5000 µg/plate (+/-S9)	There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47560020 (2007) Acceptable/guideline 0, 750, 1000, 1500, 1750, or 2150 µg/mL (+/-S9)	There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay-human peripheral blood lymphocytes	47560021 (2007) Acceptable/guideline 0, 267, 534, 1068, or 2136 µg/mL (+/-S9)	There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47560022 (2007) 0, 500, 1000, or 2000 mg/kg (limit dose)	No significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.
Aminocyclopyrachlor-methyl		
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47560033 (2005) Acceptable/Non-guideline 0, 100, 333, 1000, 3333, or 5000 µg/plate (+/-S9)	There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.

3. Structure-Activity Relationship

Aminocyclopyrachlor has three structural alerts/features (monocyclic heterocyclic aromatic amine, halogenated aromatic, nucleoside analog) of potential carcinogenic activity; however, the predictive capability of these features tends to be limited or marginal. The concern is further mitigated by the presence of a carboxylic acid moiety (which can promote rapid excretion), the ring position of chlorine (not *ortho* to ring nitrogen and therefore not a good leaving group), and the bulky cyclopropane substituent. This is supported by the submitted experimental data showing rapid excretion of the chemical and lack of genotoxicity. Overall, there is no sufficient basis for SAR concern.

4. Subchronic and Chronic Toxicity

Toxic effects of aminocyclopyrachlor and aminocyclopyrachlor-methyl via the oral route of exposure (in the diet) in subchronic (90-Day) rodent studies were limited to decreases in body weights (≤10%), body weight gains, food consumption, and food efficiency in both sexes when these compounds were administered to rats at the limit dose (1000 mg/kg/day) with no adverse effects observed in mice. Similar results were observed in chronic toxicity/carcinogenicity studies in rats and mice conducted near the limit dose. Only mild effects were observed on body weight in rats, which were limited to sporadic decreases in body weight of up to 12% that recovered by the end of the study. No adverse effects were observed in mice.

5. Mode of Action Studies

No mode of action studies were submitted.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE EVIDENCE

The Committee considered the following for a weight-of-evidence determination of the carcinogenic potential of aminocyclopyrachlor.

1. Carcinogenicity

Rat

• *Brain Tumors:* The CARC concluded that the brain tumors (glial cell tumors and granular cell tumors) observed in male rats were spontaneous lesions and were not considered to be treatment-related. This was based on the following weight-of-evidence considerations: 1) Although there were significant trends and pair-wise comparisons at the high dose for astrocytomas and glial cell tumors combined by the Peto analysis, the incidences were within the historical control range. For granular cell tumors, there was a significant trend only, but no significant pair-wise comparison of any dose group with the controls. In addition, the Fishers Exact test showed trends only and no pair-wise comparisons of any dose level with the controls for combined glial tumors and for granular cell tumors. 2) No supporting treatment-related pre-neoplastic lesions were observed in the brain (or any other tissue). (Chemicals known to cause brain tumors also are commonly tumorigenic in other tissues, J. Pletcher, Consulting Pathologist, Personal Communication); 3) The tumors occurred at the limit dose; no other tumors were seen; 4) No treatment-related brain neoplastic lesions were observed in female rats. 5) No evidence of genotoxicity was observed in *in vitro* or *in vivo* genotoxicity studies. 6) Brain levels of radioactivity after administration of aminocyclopyrachlor at times corresponding to peak plasma concentration were very low (<0.01%) and were undetectable after 72 hours.; 7) the Pathology Peer Review also concluded that the brain tumors were spontaneous tumors and not treatment-related (MRID 48333607).

• *Adequacy of Dosing:* Dosing was considered adequate, and not excessive, for assessing carcinogenicity since the high dose approached the limit dose in both sexes (892/957 mg/kg bw/day in males/females). The high dose also caused mild decreases on body weight (decrease up to 12%) and body weight gain (decrease up to 11%) in both sexes during the study, but had resolved by the conclusion of the study.

Mouse

• There were no treatment-related increases in tumor incidences in either sex.

• *Adequacy of Dosing:* Dosing was considered adequate, and not excessive, since the high dose in this study approached the limit dose (876/1190 mg/kg/day in males/females). No adverse effects (including changes in body weight) were observed at this dose level.

2. *Mutagenicity:* There is no concern for mutagenicity.

3. *SAR*: There is no sufficient basis for SAR concern.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified aminocyclopyrachlor as "Not Likely to be Carcinogenic to Humans." There were no treatment-related tumors seen in male or female rats or mice at doses that were adequate to assess carcinogenicity and there was no concern for mutagenicity.

VII. QUANTIFICATION OF CARCINOGENICITY

Quantification of carcinogenicity is not required.

VII. BIBLOGRAPHY

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